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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/911,610	07/25/2001	Shui-on Leung	018733-1053	3464

22428 7590 04/20/2006

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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 04/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/911,610	LEUNG, SHUI-ON	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20020614*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 9, 2005, has been entered.

1. The amendment filed January 26, 2006, is acknowledged and has been entered. Claim 45 has been amended.

2. Claims 44-49 are pending in the application and are currently under prosecution.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

4. The information disclosure filed June 14, 2002, has been considered. An initialed copy is enclosed.

Grounds of Objection and Rejection Withdrawn

5. Applicant's amendment and/or arguments filed August 11, 2005, or January 26, 2006, have obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed March 11, 2005.

Priority

6. Applicant's claim under 35 USC § 119(e) for benefit of the earlier filing date of the U.S. Provisional Application Serial No. 60/220,782, filed July 25, 2000, is acknowledged.

However, claims 44-49 do not properly benefit under 35 U.S.C. § 120 by the earlier filing dates of the priority documents claimed, since those claims are rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description.

To receive benefit of the earlier filing date under 35 USC §§ 119(e) and/or 120, the later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application); the disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Accordingly, the effective filing date of the claims is deemed the filing date of the instant application, namely July 25, 2001.

New Grounds of Objection

7. Claim 44 is objected to because it recites, "wherein the CL of the third binding site is those of human kappa or lambda" and "wherein the CH1 of the third binding site

is those of human IgG1". These recitations are not grammatically correct. Appropriate correction is required.

8. Claim 44 is objected to because the claim recites, "wherein cysteine is the fifth amino acid of the second polypeptide linker joined to the carboxyl terminal of CH1 of the third binding site". The claim should probably read, "wherein cysteine is the fifth amino acid of the second polypeptide linker joined to the carboxyl *terminus* of CH1 of the third binding site". Appropriate correction is required.

9. Claim 45 is objected to because the claim recites, "wherein the first amino acids of the linker joined to the carboxyl terminal of CH1 of the third binding site". The claim should probably read, "wherein the first amino acids of the linker joined to the carboxyl *terminus* of CH1 of the third binding site". Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 45-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 45-49 are indefinite because, as presently written, the claims depend from claim 1, which has been canceled. The claims fail to delineate the metes and bounds of the subject matter that Applicant regards as the invention with the requisite clarity and particularity to permit the skilled artisan to determine infringing subject matter and thereby satisfy the requirement set forth under 35 U.S.C. § 112, second paragraph.

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 44-49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Through the remainder of this Office action, in the interest of advancing prosecution, claims 45-49 have been interpreted as if the claims depend from claim 44, as opposed to claim 1.

This is a "new matter" rejection.

(a) Claim 44 recites the limitation, "wherein the CL of the third binding site is those of human kappa or lambda".

At page 4 of the amendment filed August 11, 2005, Applicant has stated that support for claim 44 is found at page 6, lines 14-19, page 14, lines 1-18, and in the figures.

Contrary to Applicant's assertion none of these disclosures or the figures provides written support for the aforementioned limitation.

Otherwise, the specification, including the claims, as originally filed, appears to provide written support for a target binding protein, according to claim 44, wherein the CL of the third binding site is a human kappa type light chain CL domain; see, e.g., page 13, paragraph 4. However, the specification, as originally filed, does not appear to provide written support for a target binding protein, according to claim 44, wherein the CL of the third binding site is a lambda type light chain CL domain.

(b) Claim 44 recites the limitation, "wherein the CH1 of the third binding site is those of human IgG1".

Again, Applicant has stated that support for claim 44 is found at page 6, lines 14-19, page 14, lines 1-18, and in the figures.

Contrary to Applicant's assertion none of these disclosures or the figures provides written support for the aforementioned limitation.

Otherwise, at page 38, paragraph 3, the specification, as originally filed, describes a genomic SacII fragment containing the human IgG1 CH1 domain, the intronic sequence connecting the CH1 to the hinge, the hinge sequence, the intronic sequence connecting the hinge to the CH2 domain, and part of the CH2 domain. The specification describes the use of this particular genomic fragment to construct a DNA molecule encoding a multivalent binding protein comprising a "hMN14" Fab molecule and two "734" scFv, which are fused to the C-terminal of the kappa chain or the C-terminal end of the Fd; see Example 1 at pages 36-40.

Because of the very specific or particular nature of this disclosure, it is not deemed sufficient to provide written support for language of the claims directed to a genus of target binding proteins, according to claim 44, wherein the CH1 of the third binding site is a CH1 domain of a human IgG1. The disclosure at page 38, paragraph 3, is not reasonably commensurate in scope with the language of the claims; and apart from this disclosure there is no other disclosure contemplating or describing the claimed genus of target binding proteins, or multivalent binding proteins as comprising a CH1 domain, which is that of human IgG1.

Moreover, while it is granted that Example 1 is meant to be exemplary of the methodology that might be used to produce the claimed product, as it is merely exemplary, it does not serve to provide written support for a limitation requiring the CH1 domain of the third binding site to be that of human IgG1, as opposed to any other CH1 domain – human or otherwise.

(c) Claim 44 recites the limitation, "wherein cysteine is the fifth amino acid of the second polypeptide linker joined to the carboxyl terminal of CH1 of the third binding site".

Again, Applicant has stated that support for claim 44 is found at page 6, lines 14-19, page 14, lines 1-18, and in the figures.

Contrary to Applicant's assertion none of these disclosures or the figures provides written support for the aforementioned limitation.

Otherwise, the specification, as originally filed, describes the second linker, which adjoins the second scFv and the immunoglobulin heavy chain constant region domain, as comprising the amino acid sequences of EPKSCGGGS (SEQ ID NO: 4) or EPKSCDKTHTCPPCPGGGS (SEQ ID NO: 2); see, e.g., page 14, paragraph 1. However, while both of these sequences have a cysteine in the fifth position, the disclosure of such linkers does not provide adequate written support for the language of the claims, which are drawn to a genus of target binding proteins, according to claim 44, which comprise a second polypeptide linker, wherein cysteine is the fifth amino acid of the second polypeptide linker joined to the carboxyl terminal of CH1 of the third binding site. The disclosures of the exemplary peptide sequences is not reasonably commensurate in scope with the language of the claims; and apart from the disclosures of these two very specific sequences, there is no other disclosure contemplating or describing the claimed genus of target binding proteins, or multivalent binding proteins as comprising a second polypeptide linker, wherein cysteine is the fifth amino acid of the second polypeptide linker joined to the carboxyl terminal of CH1 of the third binding site.

Notably, the specification further discloses, "preferably, the cysteine residue in the second peptide linker may form a disulfide bond with the CL region in a manner similar to the disulfide bond formed between an antibody light chain and heavy chain" (page 14, paragraph 1). Even so, taken altogether, these disclosures do not provide adequate written support for the language of the claims, because the latter disclosure makes no specific reference to the necessity that the cysteine residue in the second peptide linker occur at position 5 of its amino acid sequence.

(d) Claim 45 recites the limitation, "wherein the first amino acids of the linker joined to the carboxyl terminal of CH1 of the third binding site are the first five amino acids of SEQ ID NO:2".

The first five amino acids of SEQ ID NO: 2 are EPKSC. SEQ ID NO: 2 is the amino acid sequence of an exemplary second linker. The first five amino acids of SEQ ID NO: 2 are also the first five amino acids of SEQ ID NO: 4, the only other specific example of a suitable second linker; see, e.g., page 14, paragraph 1.

At page 4 of the amendment filed August 11, 2005, Applicant has stated that support for claim 45 is found at page 4, lines 1-6.

Contrary to Applicant's assertion, this particular disclosure does not appear to provide written support for the aforementioned limitation.

As presently amended, the disclosure to which Applicant has specifically referred reads as follows:

> In yet another aspect of the present invention, the first single chain Fv molecule and the immunoglobulin light chain constant region domain are covalently linked via a first peptide linker which preferably comprises the amino acid sequence EPKSADKTHTCPPCPGGGS (SEQ ID NO: 1), and the second single chain Fv and the immunoglobulin heavy chain constant region domain are covalently linked via a second peptide linker which preferably comprises the amino acid sequence EPKSCDKTHTCPPCPGGGS (SEQ ID NO: 2).

This disclosure would provide written support for claims directed to targeting protein comprising a second linker comprising the amino acid sequence of SEQ ID NO: 2, but it does not provide adequate written support for the recitation of the limitation in the claims that the first amino acids of the linker joined to the carboxyl terminal of CH1 of the third binding site are the first five amino acids of SEQ ID NO: 2.

Again, the specification, or more particularly the disclosure of the exemplary peptide sequences is not reasonably commensurate in scope with the language of the claim. Apart from the disclosure of two very specific amino acid sequences suitable for use as a "second linker" in constructing the claimed products, there is no other disclosure contemplating or describing the claimed genus of target binding proteins, or multivalent binding proteins as comprising a second polypeptide linker comprising the first amino acids of SEQ ID NO: 2.

(e) Claims 46-49 recite limitations that the three binding sites are to the same or different "epitopes".

At page 4 of the amendment filed August 11, 2005, Applicant has stated that support for claims 46-48 is found at page 4, lines 9 and 10, and page 15, lines 10, 11, and 21.

Contrary to Applicant's assertion, the particular disclosures to which they have referred do not appear to provide written support for the aforementioned limitation. The disclosures describe target binding proteins, or multivalent binding proteins having three target binding sites that have the same or different "target binding specificities". However, the fact that the three binding sites of the claimed target binding protein may have the same or different "target binding specificities" does not necessarily indicate the three binding sites are to (i.e., bind to) the same or different "epitopes", per se. As written the claims would be broadly, but reasonably be interpreted to encompass target binding proteins, or multivalent binding proteins having three target binding sites that bind the same antigen by recognition of different antigen determinants (i.e., epitopes). By the same token, the claims might be broadly, but reasonably be interpreted to encompass target-binding proteins having three target binding sites that bind the different antigens by recognition of the same antigen determinant that is common to the different antigens. Such binding sites are typically said to be "cross-reactive". When comparing the scope of the claims and the scope of the disclosures, it becomes apparent that there is disparity, which suggests the specification, as originally filed, does not provide sufficient written support for the language of the claims.

In each of the above instances, the issue might be resolved if Applicant were to point to particular disclosures in the specification, including the claims, as originally filed, which are believed to provide the necessary written support for the language of the claims.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 44-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schoonjans et al. (*Bioseparation*. 2000; 9 (3): 179-83) (of record) in view of Zuo et al. (*Protein Eng.* 2000; **13** (5): 361-367) (of record).

Claims 44-49 read on a trivalent, monospecific, bispecific or trispecific targeting binding protein comprised of two polypeptides: a first polypeptide comprised of a first scFv adjoined by a linker to the C-terminus of a human kappa or lambda light chain of an antibody and a second polypeptide comprised of a second scFv adjoined to the Fd fragment of a human IgG1 antibody, which heterodimerize to form a trifunctional binding protein by the formation of a disulfide bond between a cysteine residue of the CL domain of the light chain and the cysteine at position 5 of the partial hinge region of the Fd fragment. According to claim 49, the LV and HV domains, which form the three Fv antigen binding portions of the trifunctional molecule are derived from murine antibodies, humanized antibodies, or human antibodies.

This interpretation is reasonable because the specification defines the term "Fd" portion of an antibody as the heavy chain portion of an antibody after pepsin digestion, which comprises the VH domain, the CH1 domain, and part of the hinge region; see page 36, paragraph 5. Furthermore, the specification defines the second linker (i.e., the second extra amino acid sequence) adjoining the scFv to the C-terminus of the CH1 domain of the second fusion polypeptide as comprising "a heavy chain hinge region, or a part thereof, which has a cysteine corresponding to Cys233 according to Kabat's numbering" (page 13, paragraph 4).

Schoonjans et al. teaches trifunctional (i.e., trivalent), monospecific, bispecific or trispecific antibodies; see entire document (e.g., the abstract; page 183, column 1). Schoonjans et al. teaches these antibodies are produced as heterodimers comprised of a first fusion polypeptide comprising an scFv adjoined by a linker to the C-terminus of the light chain of an antibody and a second fusion polypeptide comprising an scFv adjoined to the C-terminus of the Fd fragment of the antibody; see, e.g., the abstract; page 180, columns 1 and 2; page 181, Figures 1 and 2; page 182, Figure 3.

Schoonjans et al. describes the production of a trivalent, trispecific antibody as a model system; see, e.g., paragraph bridging pages 182 and 183. This exemplary trifunctional antibody comprises the light chain and Fd fragment of murine monoclonal antibody E6; see, e.g., page 180, paragraph bridging columns 1 and 2). The antibody is of the IgG2b isotype; the light chain is a kappa light chain (page 180, column 2). Schoonjans et al. discloses the Fd fragment of monoclonal antibody E6 comprises the VH domain, the CH1 domain, and the first five amino acids of the adjacent, upper hinge region (page 180, column 2).

However, Schoonjans et al. does not expressly teach the production of such trivalent antibodies using human or humanized antibodies, or more particularly human or humanized IgG1 antibodies.

Zuo et al. teaches bispecific antibodies; see entire document (e.g., the abstract). Zuo et al. teaches the bispecific antibodies comprise a scFv fused to the CL domain of a human kappa light chain; see, e.g., the abstract. Zuo et al. further teaches the bispecific antibodies comprise a scFv fused to the CH1 domain of a human IgG1 antibody; see, e.g., page 362, Figure 1.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to produce a trivalent, monospecific, bispecific or trispecific targeting binding protein comprised of two polypeptides: a first polypeptide comprised of a first scFv adjoined by a linker to the C-terminus of a human kappa or lambda light chain (i.e., VL domain-CL domain) of an antibody and a second polypeptide comprised of a second scFv adjoined to the Fd fragment (i.e., VH domain-CH1 domain-first five amino acids of upper hinge region) of a human IgG1 antibody, which heterodimerize to form a trifunctional binding protein by the formation of a disulfide bond between a cysteine residue of the CL domain of the light chain and the cysteine at position 5 of the partial hinge region of the Fd fragment, because Schoonjans et al. teaches the production of functionally identical, structurally analogous proteins, which are derived in part from a murine IgG2b antibody, albeit does not expressly teach derivation from human or humanized antibodies, or more particularly from human or humanized IgG1

antibodies, whereas Zuo et al. remedies the deficiency of Schoonjans et al. suggesting derivation of such multifunctional antibodies from human IgG1 antibodies.

As evidenced by U.S. Patent No. 6,797,493 B2, the first five amino acids of the human IgG1 hinge region are the same as the first five amino acids of the amino acid sequence set forth in the application as SEQ ID NO: 2; see columns 29 and 30, SEQ ID NO: 24.

One ordinarily skilled in the art at the time of the invention would have been motivated to produce such a trivalent, monospecific, bispecific or trispecific targeting binding protein from human IgG1 molecules for use in developing means for treating diseases in humans, since, for example, Schoonjans et al. teaches multispecific antibodies are versatile tools in the development of new, experimental therapies for various diseases (page 179, column 1) and because it was well appreciated in the art at the time the invention was made that human antibodies are less immunogenic in humans, as compared to murine antibodies, and therefore better suited for use in humans.

Although none of the cited prior art references expressly teach the formation of a disulfide bond between a cysteine residue of the CL domain of the human kappa light chain and the cysteine at position 5 of the partial hinge region of the Fd fragment of the human IgG1 upon formation of the trifunctional heterodimeric targeting binding protein, the specification teaches the formation of this bond is an inherent property of such antibodies. More particular, at page 8, paragraph 2, the specification teaches:

> The CL and CH1 regions of an antibody are associated via non covalent interactions. The CL region also is linked to the hinge region of the heavy chain via a disulfide bond. For example, Cys214 (Kabat's numbering) of the kappa type of light chain can form a disulfide bond with Cys233 (Kabat's numbering) of the hinge region of the heavy chain. For Kabat's numbering, see Kabat E A, Wu T T, Perry H M, Gottesman K S and Foeller C. (1991), Sequences of proteins of immunological interest (5th edition, U.S. Dept. Health and Human Services, U.S. Government Printing Office), which is hereby incorporated by reference. The association between the CL and CH1 regions, as well as the disulfide bond between the CL region and the hinge region, contribute to the stabilization of the three-dimensional structure of an antibody.

See, also, the specification at page 13, paragraph 1: "More preferably, the cysteine residue in the second peptide linker may form a disulfide bond with the CL region **in a**

manner similar to the disulfide bond formed between an antibody light chain and heavy chain" (emphasis added). This disclosure is consistent with the position that the formation of the disulfide bond between the cysteines of the CL domain and the second linker occurs as a consequence of the intrinsic properties of the three-dimensional conformation of the two fusion polypeptides or their association as a heterodimer. Accordingly, because the trifunctional heterodimeric target binding protein disclosed, or rendered obvious by the prior art is structurally indistinguishable from that of the claimed product, it is deemed the same as the claimed product, and it is expected that the formation of the disulfide bond between a cysteine residue of the CL domain of the human kappa light chain and the cysteine at position 5 of the partial hinge region of the Fd fragment of the human IgG1 is an inherent property.

Conclusion

16. No claim is allowed.

17. The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Schoonjans et al. (*J. Immunol.* 2000 Dec 15; **165** (12): 7050-7) (of record) teaches Fab chains are efficient heterodimerization scaffolds for the production of bispecific and trispecific antibodies.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1643

slr
April 12, 2006